FINAL REPORT

A BI-COHORT STUDY OF THE RISKS OF LEFLUNOMIDE AND OTHER DMARDS IN RHEUMATOID ARTHRITIS

Samy Suissa, Ph.D.
Pierre Ernst, MD MSc
Abbas Kezouh, PhD
Alain Bitton, MD
Marie Hudson, MD

McGill University Health Centre
Montreal, Canada

Submitted to:

Dr Wanju Dai
Global Epidemiology
Aventis Pharmaceuticals
400 Crossings Boulevard
Bridgewater, NJ 08876
Tel: 908.231.3040
Fax: 908.231.2288
E-mail: wanju.dai@aventis.com

Correspondence should be addressed to:

Dr. Samy Suissa
McGill University
Director, Division of Clinical Epidemiology
Royal Victoria Hospital
687 Pine avenue west, Ross 4.29
Montréal, Québec, CANADA
H3A 1A1

Tel: 514-843-1564
Fax: 514-843-1493
E-mail: samy.suissa@clinepi.mcgill.ca

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SUMMARY

Leflunomide, a new Disease Modifying Anti-Rheumatic Drug (DMARD) introduced in 1998, has been the object of several spontaneous reports of adverse events and clinical cases described in the literature. We report on a study conducted in two large databases of health insurance claims to assess the risk of serious hepatic, dermatologic, hematologic and other adverse outcomes associated with the use of leflunomide and other DMARDS, relative to methotrexate.

We formed a retrospective cohort using data from the *Protocare* and *PharMetrics* claims databases that together encompass 26 million lives. The cohort included subjects with a diagnosis of rheumatoid arthritis who filled a prescription for a DMARD between September 1, 1998 and December 31, 2001. Cohort members were followed from the date of their first DMARD to the occurrence of serious hepatic events, hematologic events, severe skin reactions and pancreatitis, all requiring hospitalisation, as well as pneumonitis, opportunistic infection and septicemia, and lymphoma. The composite endpoint defined as the occurrence of any of the above diagnoses was used. The analysis employed a nested case-control approach with 10 to 100 randomly selected controls per case on their index date. The DMARDS dispensed during the year prior to the index date, including leflunomide, the newer biologic DMARDS and the other DMARDS were compared to monotherapy with methotrexate. Conditional logistic regression was used to estimate the rate ratio of the different endpoints, adjusted for age, gender, non-DMARD use and comorbidity.

The *PharMetrics* and *Protocare* cohorts comprised 33,009 and 8,876 users of a DMARD respectively, in which 463 cases from all causes occurred during follow-up. Overall, the rate ratio of the combined outcome of any adverse event requiring hospitalisation for leflunomide use during the year prior to the index date was 1.1 (95% CI: 0.7-1.5) while it was 1.8 (95% CI: 1.2-2.7) for biological DMARDS and 1.2 (95% CI: 0.9-1.5) for other DMARDS. While current use of leflunomide had no increased risk, past use of this medication appeared to be associated with an increased risk (RR 1.7; 95% CI: 1.0-2.9). The risk of serious hepatic events was increased only with biological DMARDS (RR 5.4: 95% CI: 1.2-24.7), while the risk of serious hematological adverse events was not increased with any DMARD. The risk of serious pancreatitis was doubled with biological DMARDS, but not with any other DMARD, inlcuding leflunomide. The risk of opportunistic infections and septicemia was doubled with biological DMARDS, but not with any other DMARD, including leflunomide. The incidence of severe skin reactions, interstitial pneumonias and lymphomas was too low to allow analyses.

Among patients with rheumatoid arthritis treated with a DMARD, we did not find an excess risk of adverse events with use of leflunomide relative to the use of methotrexate as a sir gle disease modifying therapy. The finding of an increased risk in past users of leflunomide is likely an artifact resulting from early recognition of adverse events, compensated by lower risks for current use. The study had sufficient power to detect two-fold increases in the risk of most adverse events, with the exceptions of serious pancreatitis and hepatitis for which the study could detect rate ratios of 2.5 and 5 respectively.

INTRODUCTION

Leflunomide, approved by the US Food and Drug Administration (FDA) in September 1998, was the first new Disease Modifying Anti-Rheumatic Drug (DMARD) introduced in a decade. It is indicated for adults with active rheumatoid arthritis (RA) to reduce signs and symptoms and to retard structural damage as evidenced by X-ray erosions and joint space narrowing. There have been spontaneous reports to the manufacturer and drug regulators as well as clinical cases described in the literature of adverse events in association with the use of leflunomide.

A recent study evaluated the risks of leflunomide and other DMARDS in a cohort of 40,594 patients with RA drawn from the Aetna-US Healthcare claims database covering 10 million persons (*Post-marketing cohort study of Leflunomide and other DMARDs: A comparative risk analysis, Global Epidemiology, Aventis Pharmaceuticals, March 7, 2002*). The cohort spanned the period from September 1998 through December 2000. The principal comparisons involved exposure to one and two drug combinations with leflunomide monotherapy and leflunomide with methotrexate as the reference groups. The events of interest consisted of serious hepatic events, other hepatic events, hematologic events, severe skin reactions, hypertension, vasculitis and hemolytic anemia, pneumonitis, pancreatitis, gastrointestinal bleeding, respiratory events, and septic arthritis, as well as a composite outcome of any of these events. That study found that the rates of these events with leflunomide exposure were statistically lower or no different than for the reference. The results are limited by the lack of more intricate analyses of the cohort, due to the restricted access to the raw database.

We report on another study conducted in two large databases of health insurance claims to assess the risk of serious hepatic, dermatologic, hematologic and other adverse outcomes associated with the use of leflunomide and other DMARDS, relative to methotrexate.

METHODS

Study Design and Data Source

We formed a retrospective cohort, based on two sources of data, to evaluate these risks. The first data source is a subset of the *Protocare* longitudinal health benefit claims database that combines data from Medicaid, Medicare, private health maintenance organizations (HMO) and preferred provider organizations (PPO). This proprietary database encompasses over 10 million lives and has been in existence since 1991. The second source of data is the *PharMetrics* Integrated Outcomes Database. It consists of standardized information on claims data from over 40 different managed care organizations and encompasses more than 16 million lives. For the present study, the two datasets were limited to claims with at least one occurrence of a diagnosis of rheumatoid arthritis (ICD-9: 714) between January 1, 1998 and December 31, 2001. These databases do not permit access to the medical records so as to protect patient confidentiality.

Because of the complexity in the patterns of drugs used to treat RA, the risks were estimated using a nested case-control approach. This allows one to deal effectively with multiple drug use and varying durations of use.

Cohort Definition

Cohort entry was defined for both cohorts by the date of the first prescription for a DMARD after September 1, 1998, the launching date of leflunomide in the US. The DMARDs include leflunomide, methotrexate, gold compounds, anti-tumor necrosis factor alpha agents (anti-TNF), antimalarials, minocycline, chelating agents, sulfasalazine and cytotoxics. All subjects were followed from the date of the first prescription until the earliest of: the date of termination of enrollment in the health plan, the date of death, the end of the study period (December 31, 2001) or the date of the clinical outcome of interest. Subjects had to be eighteen years or older at cohort entry. Subjects with less than three months of eligibility in the health insurance plan prior to cohort entry were excluded. In addition, subjects with the outcome of interest during the three-month period prior to cohort entry were excluded.

Outcome Events

Outcome events were identified from inpatient and outpatient encounters, using specific ICD-9 codes (see Appendix A). The events under study include serious hepatic events (hepatic nécrosis, cirrhosis, hepatic coma, and hepatitis), hematologic events (aplastic anemia, agranulocytosis, pancytopenia), severe skin reactions (erythema multiformae, Stevens-Johnson Syndrome, toxic epidermal necrolysis), and pancreatitis all requiring hospitalisation, as well as pneumonitis, opportunistic infection and septicemia, and lymphoma. We also evaluated the same endpoints without the requirement for hospitalisation (expanded definition).

Because of the rarity of some of these outcomes, a composite endpoint, defined as the occurrence of ***any*** of the above diagnoses, was created. For subjects with more than one endpoint, the first occurrence during follow-up was used.

Nested case-control design

We used a nested case-control design within the cohorts. This approach allows us to address the complex patterns of drug exposure with insignificant loss of power. For each case identified in the cohorts, we randomly selected 10 controls from the cohort, after matching on the date of cohort entry and ensuring that they were at risk on the day of the event of the case. That date was designated the index date. For the events with few cases (less than 100), we increased the number of controls to 100 per case.

Exposure Measurement

All drugs received during follow-up, including DMARDS and other non-DMARD RA drugs, were identified from dispensed prescription data. The type, date of filling, and the duration of each prescription dispensed at the time of cohort entry were obtained from the databases.

For the purposes of comparison, the DMARDS were divided into four groups: leflunomide, the newer biologic DMARDS (TNF receptor antagonists: inflixmab and etanercept), the other DMARDS (gold compounds, antimalarials, minocycline, chelating agents, sulfasalazine and cytotoxics; these include auranofin, aurothioglucose, gold sodium thiomalate, hydroxychloroquine, hydroxychloroquine sulfate, minocycline, penicillamine, sulfasalazine, chlorambucil, cyclophosphamide and cyclosporine) and methotrexate (including methotrexate sodium). Methotrexate was used as the reference drug in all comparisons. The other non-DMARD anti-RA drugs, namely glucocorticoids,

non-steroidal anti-inflammatory drugs (NSAIDS) and COX-2 inhibitors, were not used as exposure but rather as covariates.

Covariate information

Age, gender and the source of data (Protocare or Pharmetrics) were used as basic covariates that define the study population. The assessment of comorbid conditions was based on diagnoses made during the observation period. These included cardiovascular disease (ICD-9: 391-400, 402-404, 410-429, 430-453), respiratory illness (ICD-9: 480-519), diabetes (ICD-9: 250), hypertension (ICD-9: 401), hypercholesterolemia (ICD-9: 272.0), cancer(ICD-9: 140-208, 230-239), gastrointestinal conditions (ICD-9: 530-537,555-558), vasculitis (ICD-9: 446.20,446.29,273.2,287,0) and CNS conditions (ICD-9: 320-389). As mentioned above, non-DMARD drugs used for symptomatic relief, namely glucocorticoids, NSAIDS and COX-2 inhibitors, were also used as covariates to control for disease severity.

Data analysis

Total person-time of follow-up in the 2 cohorts was cumulated to estimate the rate of adverse events for each endpoint, including the composite endpoint, under study. Conditional logistic regression was used with the nested case-control samples to estimate the rate ratio of the different endpoints, including the composite, for any use of leflunomide, newer DMARDS and other DMARDS, all relative to methotrexate monotherapy, during the year prior to the index date. Non-use of any DMARD during the one-year period was accounted for in the analysis to maintain the same reference group across comparisons. Leflunomide exposure was further redefined in two ways. First, current use of leflunomide was defined by the last prescription prior to the index date being dispensed within 90 days of the index date, while any other use during the year prior to the index date was designated as past use. Second, the use of leflunomide during the year prior to the index date was separated as monotherapy or multitherapy if other DMARDs were dispensed at any time during that year. All analyses were adjusted for the concurrent use of other DMARDS, the non-DMARDS, namely glucocorticoids, NSAIDS and COX-2 inhibitors, as well as age, gender and co-morbidity.

RESULTS

There were 96,738 subjects in the *PharMetrics* database and 32,063 in the *Protocare* database with at least one occurrence of the diagnosis of rheumatoid arthritis between January 1, 1998 and December 31, 2001. After excluding subjects who were not dispensed a DMARD, who had less than three months of eligibility in the health insurance plan prior to cohort entry, or with outcome of interest prior to cohort entry, the *PharMetrics* cohort comprised 33,009 subjects who received a DMARD after September 1, 1998, while the *Protocare* cohort had 8,876 subjects. The characteristics of the subjects at cohort entry are displayed in Table 1 for both cohorts. Subjects from the Protocare cohort were 10 years older than those from the Pharmetrics cohort.

The *PharMetrics* cohort was followed for a total of 39,286 person-years, while the *Protocare* cohort had 12,029 person-years of follow-up. There were 463 cases of serious adverse events from all causes in the two combined cohorts, 295 in Pharmetrics and 168 in Protocare. Table 2 shows that the rate of any such adverse event was 75 per 10,000

per year in the Pharmetrics cohort and 140 per 10,000 per year in the older Protocare cohort. Rates are also given for specific events. Of note is the small number of severe skin reactions, pneumonitis and lymphomas.

Table 3 provides descriptive information for these cases and their respective controls in both cohorts. Overall, the cases in the Protocare cohort are more than 10 years older than in the Pharmetrics cohort. Follow-up in the Protocare cohort was also longer, 371 days compared to 302 days in the Pharmetrics cohort. The majority of subjects with rheumatoid arthritis were women. A significant proportion of patients had been dispensed glucocorticoids during the year prior to the index date and this was more likely to have occurred among cases than controls in both cohorts. Comorbidity was common and more so among subjects in the Protocare cohort, who were older, and more common in case patients than control patients in both cohorts. The principal comorbidities during the year prior to the index date were cardiovascular diseases, hypertension, CNS complaints, respiratory diseases and diabetes.

Table 4 presents adjusted rate ratios of the combined outcome of any adverse event requiring hospitalisation for disease modifying anti-rheumatoid arthritis drugs compared with the use of methotrexate as the only disease modifying drug. Overall, in the Pharmetrics cohort there was an increase in the risk of any such adverse event for biological DMARDS (RR 1.8). There was no statistically significant increase in the risk of all adverse events combined in either of the cohorts with leflunomide. An exception was with the past use of this medication, as measured by use during the 9-month period preceding the last 90 days prior to the index date. This excess risk with past use of leflunomide was present in both databases.

When examining the risk of serious hepatic events requiring hospitalisation, the number of cases was low so that 100 controls per case had to be selected. In the Pharmetrics cohort, none of the 11 cases of these hepatic events were exposed to leflunomide and only 2 of the 14 in the Protocare cohort (Table 5). When combining the two cohorts, there is a suggestion of an increased risk of hepatic events requiring hospitalisation with the use of biological DMARDS (RR 5.4; 95% CI: 1.2-24.7) and possibly with the other DMARDS (RR 2.3) as compared to the risk for patients receiving methotrexate as the only disease modifying anti-rheumatoid arthritis drug.

When addressing the risk of hematological adverse events requiring hospitalisation (Table 6), the numbers of cases were relatively small (88 and 50 cases in the Pharmetrics and Protocare cohorts, respectively) and therefore required 100 controls per case. Considering the cohorts together, all rate ratios were below 1.0 for leflunomide. There was also no excess risk demonstrable for biological DMARDS or other DMARDS .

In examining the risk of pancreatic events requiring hospitalisation (Table 7), here again the limited number of cases (46 and 38 cases in the Pharmetrics and Protocare cohorts, respectively) justified the use of 100 controls per case. Past use of leflunomide appears associated, although not significantly so, with an increased risk compared with the use Methotrexate as the only disease modifying agent. An increase in risk of similar size was seen with biological DMARDS.

For the risk of opportunistic infections and septicemia requiring hospitalisation (Table 8) there was no statistically significant increase in risk for any or past use of leflunomide when the cohorts were combined. The use of biological DMARDS was associated with a two-fold increase in risk of opportunistic infections and septicemia requiring hospitalisation. Given that severe opportunistic infections and septicemia would

be expected to result in hospitalisation, we did not examine such events in the absence of a hospitalisation.

The incidence of severe skin reactions was extremely small, with only 3 cases requiring hospitalisation, none of which used leflunomide, so that no analyses could be carried out (Table 9). Interstitial pneumonias (pneumonitis) requiring hospitalisation occurred in insufficient numbers (12 cases overall) to allow an analysis of the risk in association with use of disease modifying medications, although one case was exposed to leflunomide (Table 10). Similarly, among the 5 lymphoma cases, none occurred among subjects on leflunomide, while too few cases were seen amongst patients prescribed methotrexate only, biological DMARDS, or other DMARDS to allow any analyses (Table 11).

Appendix B provides these tables separately for the two cohorts, as well as combined. The similarity of findings in the two cohorts justifies the combined analysis.

Similar findings were observed when examining the risk of these adverse events without requiring the need for hospitalisation (see Appendix C). Only for pancreatic events not requiring hospitalisation (Table C.11) was leflunomide associated with a 70% increase in risk, slightly more marked with monotherapy and past use. For this same outcome, there was an approximately 50% increase in risk for biological DMARDS and other DMARDS with only the latter achieving statistical significance when combining the two cohorts.

DISCUSSION

In two large cohorts of patients with rheumatoid arthritis treated with a DMARD, we did not find an excess risk of adverse events among users of leflunomide, particularly the current users, relative to users of methotrexate as monotherapy

When examining specific adverse events, the number of events where hospitalisation occurred was too small to produce informative analyses for severe skin reactions, interstitial pneumonias and lymphomas. Except for one case of interstitial pneumonia, however, no cases had been exposed to leflunomide. For hepatic and hematological events, pancreatitis and opportunistic infections and septicemia requiring hospitalisation, the number of cases varied between 25 and 138 cases. By increasing the number of controls per case, we were able to increase the power and obtain stable risk estimates. For hepatic adverse events and opportunistic infections and septicemia requiring hospitalisation, no risk was found with leflunomide. For hematological events and pancreatitis, there was a small increase in risk with leflunomide, although the risk was mostly limited to past users.

The finding of a 70% increase in the risk of all adverse events combined with past use of leflunomide, mostly observed for hematological events and pancreatitis, is likely an artifact. We believe it most probably represents cessation of the drug by patients or their physician because of approaching adverse events that were recognized. Even for very acute events, note that while past use is defined by the date of the last drug being dispensed more than 90 days before the index date, its use could have continued into that 90-day period and stopped close to the index date. Moreover, the increase observed with past use is compensated by a rate ratio for current use lower than unity. For these reasons, the evaluation of the risk using the one-year period prior to the index date is a more reliable approach that is less likely to be influenced by such actions. Alternatively, of course, this higher rate with past use with borderline statistical significance (RR 1.7; 95% CI: 1.0-2.9) could also simply be due to random error.

We found an 80% increase in the risk of all adverse events requiring hospitalisation associated with the use of biological DMARDs, although this risk was attenuated when the case definition did not require hospitalisation. For hepatic and hematological events, pancreatitis, opportunistic infections and septicemia, we found an increase in risk with biological DMARDS. This small but systematic increase in the risk of all these events was not the object of the current study but requires further investigation. In particular, it should be noted that no analyses were planned or conducted for specific patterns of use for biological DMARDS; such as past use or multitherapy. In any case, such analyses would not have been possible for biological DMARDS because of their later introduction on the market and the small number of subjects that were prescribed these medications in this study. Nevertheless, future research should address these adverse effects.

The current study has several limitations. Firstly, the number of certain adverse events was small, so that it was not possible to study events such as severe skin reactions, interstitial pneumonias and lymphomas. We clearly had sufficient power (80%), however, to detect a rate ratio of 1.5 with leflunomide use for the combined outcome of any adverse event requiring hospitalisation and a rate ratio of 1.2 without requiring hospitalisation. The power was also sufficient to detect a rate ratio of 1.5 for hepatitis without requiring hospitalisation and hematological events not requiring hospitalisation. However, for hepatitis requiring hospitalisation, the study only had sufficient power to detect rate ratios of 5 or more. For pancreatitis requiring hospitalisation, rate ratios of 2.5 could be detected from our study. Finally, for hematological events and opportunistic infections and septicemia requiring hospitalisation, as well as for pancreatitis not requiring hospitalisation, rate ratios of 2 could be detected with 80% power. Thus, overall, this study provides high confidence in excluding a doubling of the risk of most adverse events, and particularly the combined outcome, associated with leflunomide use. The only exceptions are pancreatitis and hepatitis both requiring hospitalisation for which the study can only provide assurance for rate ratios of 2.5 and 5 respectively. A strength of the study that serves to validate the results is the use of two independent cohorts and the marked consistency of findings across the two cohorts. In addition, the various populations represented in the cohorts including Medicaid, Medicare, private health maintenance organizations and preferred provider organizations and over 40 different managed care organizations provide further consistency to the findings.

Because of the relatively short duration of follow-up, it was unfeasible to evaluate long-term effects of these drugs. Nevertheless, the cohorts had an average follow-up of around one year and up to three years. Moreover, by extending the follow-up to December 2001, the study included the most recent available data to assess the safety of leflunomide. In this study, we could not verify the validity of the diagnoses used to identify adverse events. The differences in the incidence of these events in the two cohorts (8.9 versus 18.9 per 1000 for Pharmetrics and Protocare respectively) could suggest that the diagnostic criteria used were not uniform in the two cohorts. However, age alone may explain these differences. In fact, a strong element of validation of the diagnoses is the marked uniformity in the results across the two cohorts for all adverse events. A further limitation of our study is the possibility of residual confounding. The associations between adverse events and the various medications used may have been attenuated or increased if physicians prescribed certain of these medications in subset of patients with or without risk factors for these adverse events. For instance, biological DMARDS may have been preferentially prescribed to subjects with known susceptibility for liver disease. We

attempted to reduce this form of confounding by restricting the analyses to cases and controls who did not have the adverse event under study prior to cohort entry. We also adjusted for co-morbidity that could confound these risk estimates.

In conclusion, in this large bi-cohort study, we did not find an excess risk of serious adverse events with the use of leflunomide relative to methotrexate in patients with rheumatoid arthritis treated with a DMARD. The small but systematic increase in risk observed with biological DMARDS requires further investigation.

Table 1

Characteristics of subjects at cohort entry

	Pharmetrics (n=33,009)	Protocare (n=8,876)
Follow-up (mean in days)	436	499
Age (mean in years)	49	59
Gender (% male)	24%	24%
DMARD at cohort entry:		
Methotrexate	45%	56%
Leflunomide	7%	6%
Biologic DMARDS	5%	1%
Other DMARDS	43%	37%
Leflunomide use at any time during follow-up	16%	14%

Table 2

Overall rates (per 10,000 per year) of serious adverse events under study for the Pharmetrics and Protocare cohorts separately and combined

	Pharmetrics (39,285.8 person-years)		Protocare (12,029.2 person-years)		Combined (51,315.0 person-years)	
	Number	Rate	Number	Rate	Number	Rate
Any event	295	75.09	168	139.66	463	90.23
Hepatic	11	2.80	14	11.64	25	4.87
Hematologic	88	22.40	50	41.57	138	26.89
Pancreatic	46	11.71	38	31.59	84	16.37
Opportunistic infections and septicemia	153	38.95	62	51.54	215	41.90
Severe skin reactions	3	0.76	0	0.00	3	0.58
Pneumonitis	3	0.76	9	7.48	12	2.34
Lymphoma	3	0.76	2	1.66	5	0.97

Table 3

Comparison of cases of any serious adverse event and controls on characteristics, concurrent other drug use and co-morbidity from the Pharmetrics and Protocare cohorts

	Pharmetrics		Protocare	
	Cases	Controls	Cases	Controls
Number	295	2950	168	1680
Age	53 ± 12	50 ± 11	64 ± 13	61 ± 14
Follow-up (days)	302 ± 257	302 ± 256	372 ± 248	371 ± 247
Gender (% male)	22%	24%	19%	22%
Other RA drugs				
NSAIDs	29%	39%	34%	43%
Cox-2 inhibitors	23%	22%	14%	13%
Glucocorticoids	40%	28%	38%	31%
Concurrent diseases				
Cardiovascular	40%	17%	62%	25%
Respiratory	42%	17%	51%	19%
Diabetes	17%	8%	24%	13%
Hypertension	27%	18%	15%	13%
Hypercholesterolemia	9%	11%	21%	18%
Cancer	20%	8%	26%	12%
Gastrointestinal	22%	11%	27%	17%
CNS conditions	49%	37%	45%	34%
Vasculatis	<1%	<1%	<1%	<1%

Table 4

Crude and adjusted rate ratios of any serious adverse event for newer DMARDs relative to methotrexate monotherapy from the combined cohorts

DMARD use in the prior year	Cases (n=463)	Controls (n=4630)	Crude RR	Adjusted* RR	Adjusted* 95% CI
Methotrexate only	158	1771	1.0	1.0	Reference
Leflunomide	53	554	1.1	1.1	0.7-1.5
Monotherapy	26	268	1.1	1.0	0.6-1.6
Multitherapy	27	286	1.1	1.1	0.7-1.7
Current use	32	416	0.9	0.8	0.6-1.3
Past use	21	138	1.7	1.7	1.0-2.9
Biologic DMARDS	37	298	1.4	1.8	1.2-2.7
Other DMARDS	184	1729	1.2	1.2	0.9-1.5

* Adjusted for age, gender, cohort, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table 5

Crude and adjusted rate ratios of serious hepatic events for newer DMARDs relative to methotrexate monotherapy

DMARD use in the prior year	Cases (n=25)	Controls (n=2500)	Crude RR	Adjusted* RR	Adjusted* 95% CI
Methotrexate only	7	989	1.0	1.0	Reference
Leflunomide	2	270	1.1	0.9	0.2-4.9
Monotherapy	0	117	0.0	0.0	ne
Multitherapy	2	153	1.9	1.6	0.3-8.7
Current use	0	194	0.0	0.0	ne
Past use	2	76	3.8	2.6	0.4-15.5
Biologic DMARDS	4	128	5.2	5.4	1.2-24.7
Other DMARDS	12	911	1.9	2.3	0.8-6.6

* Adjusted for age, gender, cohort, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table 6

Crude and adjusted rate ratios of serious hematologic events for newer DMARDs relative to methotrexate monotherapy

DMARD use in the prior year	Cases (n=138)	Controls (n=13684)	Crude RR	Adjusted* RR	95% CI
Methotrexate only	62	5250	1.0	1.0	Reference
Leflunomide	17	1624	0.9	0.8	0.5-1.5
Monotherapy	8	785	0.9	0.8	0.3-1.6
Multitherapy	9	839	0.9	0.9	0.4-1.9
Current use	13	1210	0.9	0.9	0.5-1.7
Past use	4	414	0.8	0.7	0.2-1.9
Biologic DMARDS	10	814	1.1	1.2	0.6-2.4
Other DMARDS	40	5059	0.7	0.7	0.5-1.0

* Adjusted for age, gender, cohort, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table 7

Crude and adjusted rate ratios of serious pancreatitis events for newer DMARDs relative to methotrexate monotherapy

DMARD use in the prior year	Cases (n=84)	Controls (n=8394)	Crude RR	Adjusted* RR	Adjusted* 95% CI
Methotrexate only	25	3152	1.0	1.0	Reference
Leflunomide	11	996	1.4	1.5	0.7-3.1
Monotherapy	6	461	1.7	1.7	0.7-4.2
Multitherapy	5	535	1.2	1.3	0.5-3.5
Current use	6	730	1.1	1.1	0.5-2.8
Past use	5	266	2.5	2.4	0.9-6.5
Biologic DMARDS	8	542	2.0	2.2	1.0-5.3
Other DMARDS	31	3089	1.3	1.4	0.8-2.4

* Adjusted for age, gender, cohort, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table 8

Crude and adjusted rate ratios of serious opportunistic infections & septicemia events for newer DMARDs relative to methotrexate monotherapy

DMARD use in the prior year	Cases (n=215)	Controls (n=7729)	Crude RR	Adjusted* RR	Adjusted* 95% CI
Methotrexate only	63	3224	1.0	1.0	Reference
Leflunomide	25	888	1.1	0.9	0.6-1.6
Monotherapy	12	452	1.0	0.8	0.4-1.6
Multitherapy	13	436	1.2	1.1	0.6-2.1
Current use	14	638	0.9	0.7	0.4-1.4
Past use	11	250	1.9	1.4	0.7-2.9
Biologic DMARDS	18	197	1.5	2.0	1.1-3.6
Other DMARDS	95	2958	1.3	1.2	0.9-1.7

* Adjusted for age, gender, cohort, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table 9

Frequency of severe skin reactions for newer DMARDs and methotrexate monotherapy (Rate ratios are not estimable)

DMARD use in the prior year	Cases (n=3)	Controls (n=30)
Methotrexate only	0	10
Leflunomide	0	3
Monotherapy	0	2
Multitherapy	0	1
Current use	0	2
Past use	0	1
Biologic DMARDS	0	2
Other DMARDS	3	15

Table 10

Frequency of pneumonitis for newer DMARDs and methotrexate monotherapy (Rate ratios are not estimable)

DMARD use in the prior year	Cases (n=12)	Controls (n=120)
Methotrexate only	4	52
Leflunomide	1	13
Monotherapy	1	4
Multitherapy	0	9
Current use	1	7
Past use	0	6
Biologic DMARDS	0	4
Other DMARDS	6	40

Table 11

Frequency of lymphoma
for newer DMARDs and methotrexate monotherapy
(Rate ratios are not estimable)

DMARD use in the prior year	Cases (n=5)	Controls (n=50)
Methotrexate only	0	14
Leflunomide	0	8
Monotherapy	0	3
Multitherapy	0	5
Current use	0	4
Past use	0	4
Biologic DMARDS	1	4
Other DMARDS	3	18

Appendix A

Endpoint Definitions

Hepatic Events,requiring hospitalization

Acute or Subacute Liver Necrosis (ICD-9CM : 570)
Cirrhosis of liver without mention of alcohol (ICD-9CM 571.5)
Hepatitis, Noninfectious Toxic (ICD-9CM : 573.3)
Hepatic Coma (ICD-9CM : 572.2)

Hematologic,requiring hospitalization

284.8	Other specified aplastic anemias Aplastic anemia (due to): chronic systemic disease drugs infection radiation toxic (paralytic) Pancytopenia (acquired) Red cell aplasia (acquired) (adult) (pure) (with thymoma)
284.9	Aplastic anemia, unspecified Anemia: aplastic (idiopathic) NOS aregenerative hypoplastic NOS nonregenerative refractory Medullary hypoplasia
287.4	Secondary thrombocytopenia Posttransfusion purpura Thrombocytopenia due to: Dilutional Drugs Extracorporeal circulation of blood Platelet alloimmuinzation
288.0	Agranulocytosis

Severe Skin Reactions,requiring hospitalization

695.1	Erythema multiforme Erythema iris Herpes iris Lyell's syndrome Scalded skin syndrome Stevens-Johnson syndrome Toxic epidermal necrolysis

Hypertension,requiring hospitalization

401.0 Malignant Essential hypertension
401.9 Unspecified Elevated blood pressure

Vasculitis

446.20 Hypersensitivity angiitis
446.29 Other specified hypersensitivity angiitis
273.2 Other paraproteinemias: cryglobulinemic purpura or vasculitis
287.0 Allergic purpura

Pneumonitis

495.9 Unspecified allergic alveolitis and pneumonitis
515 Post-inflammatory pulmonary fibrosis
516.8 Other specified alveolar and parietoalveolar pneumonopathies

in conjunction with:
32.28 lung biopsy (open)
32.37 lung biopsy (closed)

Pancreatitis,requiring hospitalization

577.0 Acute pancreatitis
Abscess of pancreas
Necrosis of pancreas:
acute
infective
Pancreatitis:
NOS
acute (recurrent)
apoplectic
hemorrhagic
subacute
suppurative

Lymphoma

202 Other malignant neoplasms of lymphoid and histiocytic tissue

Opportunistic Infections & Septicemia

010-018 tuberculosis
031 diseases due to mycobacteria
038 septicemia
136.3 pneumocystosis

APPENDIX B

COMPARATIVE RESULTS BY COHORT AND COMBINED

Table B.1

Crude and adjusted rate ratios of any serious adverse event for newer DMARDs relative to methotrexate monotherapy

	PHARMETRICS				PROTOCARE				COMBINED			
DMARD use in the prior year	Cases (n=295)	Controls (n=2950)	Crude RR	Adjusted* RR (95% CI)	Cases (n=168)	Controls (n=1680)	Crude RR	Adjusted* RR (95% CI)	Cases (n=463)	Controls (n=4630)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	77	975	1.0	Reference	81	796	1.0	Reference	158	1771	1.0	Reference
Leflunomide	35	384	1.2	1.1 (0.7-1.7)	18	170	1.0	1.0 (0.6-1.9)	53	554	1.1	1.1 (0.7-1.5)
Monotherapy	19	194	1.2	1.1 (0.7-2.0)	7	74	0.9	0.9 (0.4-2.1)	26	268	1.1	1.0 (0.6-1.6)
Multitherapy	16	190	1.1	1.1 (0.6-2.0)	11	96	1.1	1.2 (0.6-2.5)	27	286	1.1	1.1 (0.7-1.7)
Current use	20	293	0.9	0.8 (0.5-1.4)	12	123	1.0	0.9 (0.5-1.9)	32	416	0.9	0.8 (0.6-1.3)
Past use	15	91	2.1	2.0 (1.1-3.8)	6	47	1.3	1.3 (0.5-3.6)	21	138	1.7	1.7 (1.0-2.9)
Biologic DMARDS	35	286	1.6	1.9 (1.2-3.0)	2	12	1.7	1.6 (0.3-8.6)	37	298	1.4	1.8 (1.2-2.7)
Other DMARDS	127	1148	1.4	1.4 (1.0-1.9)	57	581	1.0	1.0 (0.7-1.5)	184	1729	1.2	1.2 (0.9-1.5)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table B.2

Crude and adjusted rate ratios of any hepatic event for newer DMARDs relative to methotrexate monotherapy

DMARD use in the prior year	PHARMETRICS				PROTOCARE				COMBINED			
	Cases (n=11)	Controls (n=1100)	Crude RR	Adjusted* RR (95% CI)	Cases (n=14)	Controls (n=1400)	Crude RR	Adjusted* RR (95% CI)	Cases (n=25)	Controls(n=2500)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	2	364	1.0	Reference	5	625	1.0	Reference	7	989	1.0	Reference
Leflunomide	0	117	0.0	0.0 (ne)	2	153	1.6	1.8 (0.3-11.8)	2	270	1.1	0.9 (0.2-4.9)
Monotherapy	0	56	0.0	0.0 (ne)	0	61	0.0	0.0 (ne)	0	117	0.0	0.0 (ne)
Multitherapy	0	61	0.0	0.0 (ne)	2	92	2.8	3.5(0.5-23.0)	2	153	1.9	1.6(0.3-8.7)
Current use	0	81	0.0	0.0 (ne)	0	113	0.0	0.0 (ne)	0	194	0.0	0.0 (ne)
Past use	0	36	0.0	0.0 (ne)	2	40	6.4	15.0 (2.2-103.6)	2	76	3.8	2.6 (0.4-15.5)
Biologic DMARDS	2	119	3.0	3.6 (0.4-35.5)	2	9	35.0	34.0(2.5-471.3)	4	128	5.2	5.4 (1.2-24.7)
Other DMARDS	7	401	3.2	4.4 (0.8-25.6)	5	510	1.3	1.5 (0.3-6.4)	12	911	1.9	2.3 (0.8-6.6)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table B.3

Crude and adjusted rate ratios of any hematologic event for newer DMARDs relative to methotrexate monotherapy

DMARD use in the prior year	PHARMETRICS				PROTOCARE				COMBINED			
	Cases (n=88)	Controls (n=8795)	Crude RR	Adjusted* RR (95% CI)	Cases (n=50)	Controls (n=4889)	Crude RR	Adjusted* RR (95% CI)	Cases (n=138)	Controls (n=13684)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	34	2965	1.0	Reference	28	2285	1.0	Reference	62	5250	1.0	Reference
Leflunomide	11	1096	0.9	0.8(0.4-1.7)	6	528	0.9	0.8 (0.3-2.1)	17	1624	0.9	0.8 (0.5-1.5)
Monotherapy	6	539	1.0	0.9 (0.4-2.2)	2	246	0.7	0.5 (0.1-2.2)	8	785	0.9	0.8 (0.3-1.6)
Multitherapy	5	557	0.8	0.8 (0.3-2.1)	4	282	1.2	1.2 (0.4-3.6)	9	839	0.9	0.9 (0.4-1.9)
Current use	8	815	0.9	0.9 (0.4-1.9)	5	395	1.1	0.9 (0.3-2.5)	13	1210	0.9	0.9 (0.5-1.7)
Past use	3	281	0.9	0.8 (0.2-2.7)	1	133	0.6	0.5 (0.1-4.0)	4	414	0.8	0.7 (0.2-1.9)
Biologic DMARDS	9	769	1.0	1.1 (0.5-2.5)	1	45	1.9	2.0(0.2-18.6)	10	814	1.1	1.2 (0.6-2.4)
Other DMARDS	27	3367	0.7	0.7 (0.4-1.2)	13	1692	0.6	0.6 (0.3-1.2)	40	5059	0.7	0.7 (0.5-1.0)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table B.4

Crude and adjusted rate ratios of any pancreatitis event for newer DMARDs relative to methotrexate monotherapy

DMARD use in the prior year	PHARMETRICS				PROTOCARE				COMBINED			
	Cases (n=46)	Controls (n=4600)	Crude RR	Adjusted* RR (95% CI)	Cases (n=38)	Controls (n=3794)	Crude RR	Adjusted* RR (95% CI)	Cases (n=84)	Controls (n=8394)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	8	1440	1.0	Reference	17	1712	1.0	Reference	25	3152	1.0	Reference
Leflunomide	5	634	1.5	1.5 (0.5-4.7)	6	362	1.7	1.7 (0.7-4.7)	11	996	1.4	1.5 (0.7-3.1)
Monotherapy	4	328	2.2	2.2 (0.6-7.5)	2	133	1.5	1.6 (0.3-7.4)	6	461	1.7	1.7 (0.7-4.2)
Multitherapy	1	306	0.6	0.7 (0.1-5.5)	4	229	1.8	1.8 (0.6-5.8)	5	535	1.2	1.3 (0.5-3.5)
Current use	2	470	0.8	0.8 (0.2-3.8)	4	260	1.6	1.7 (0.6-5.5)	6	730	1.1	1.1 (0.5-2.8)
Past use	3	164	3.6	3.9 (1.0-15.6)	2	102	2.0	1.7 (0.4-8.0)	5	266	2.5	2.4 (0.9-6.5)
Biologic DMARDS	8	485	3.2	3.3 (1.2-9.3)	0	57	0.0	0.0(ne)	8	542	2.0	2.2 (1.0-5.3)
Other DMARDS	20	1749	2.1	2.2(0.9-5.0)	11	1340	0.8	0.9 (0.4-2.0)	31	3089	1.3	1.4 (0.8-2.4)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table B.5

Crude and adjusted rate ratios of any opportunistic infections & septicemia event for newer DMARDs relative to methotrexate monotherapy

	PHARMETRICS				PROTOCARE				COMBINED			
DMARD use in the prior year	Cases (n=153)	Controls (n=1530)	Crude RR	Adjusted* RR (95% CI)	Cases (n=62)	Controls (n=6199)	Crude RR	Adjusted* RR (95% CI)	Cases (n=215)	Controls (n=7729)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	33	491	1.0	Reference	30	2733	1.0	Reference	63	3224	1.0	Reference
Leflunomide	21	199	1.6	1.3 (0.7-2.5)	4	689	0.5	0.5 (0.2-1.4)	25	888	1.1	0.9 (0.6-1.6)
Monotherapy	10	106	1.4	1.0 (0.5-2.3)	2	346	0.5	0.5 (0.1-2.2)	12	452	1.0	0.8 (0.4-1.6)
Multitherapy	11	93	1.8	1.7 (0.8-3.8)	2	343	0.5	0.5 (0.1-2.0)	13	436	1.2	1.1 (0.6-2.1)
Current use	11	150	1.1	1.0 (0.4-2.1)	3	488	0.6	0.5 (0.2-1.8)	14	638	0.9	0.7 (0.4-1.4)
Past use	10	49	3.2	2.4 (1.0-5.8)	1	201	0.5	0.4 (0.1-3.0)	11	250	1.9	1.4 (0.7-2.9)
Biologic DMARDS	18	139	2.0	2.8 (1.4-5.5)	0	58	0.0	0.0 (ne)	18	197	1.5	2.0 (1.1-3.6)
Other DMARDS	72	627	1.7	1.6(1.0-2.6)	23	2331	0.9	0.9 (0.5-1.5)	95	2958	1.3	1.2 (0.9-1.7)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table B.6

Frequency of severe skin reactions for newer DMARDs and methotrexate monotherapy (Rate ratios not estimable)

DMARD use in the prior year	PHARMETRICS		PROTOCARE		COMBINED	
	Cases (n=3)	Controls (n=30)	Cases (n=0)	Controls (n=0)	Cases (n=3)	Controls (n=30)
Methotrexate only	0	10	0	0	0	10
Leflunomide	0	3	0	0	0	3
Monotherapy	0	2	0	0	0	2
Multitherapy	0	1	0	0	0	1
Current use	0	2	0	0	0	2
Past use	0	1	0	0	0	1
Biologic DMARDS	0	2	0	0	0	2
Other DMARDS	3	15	0	0	3	15

Table B.7

Frequency of pneumonitis
for newer DMARDs and methotrexate monotherapy
(Rate ratios not estimable)

DMARD use in the prior year	PHARMETRICS		PROTOCARE		COMBINED	
	Cases (n=3)	Controls (n=30)	Cases (n=9)	Controls (n=90)	Cases (n=12)	Controls (n=120)
Methotrexate only	1	13	3	39	4	52
Leflunomide	0	4	1	9	1	13
Monotherapy	0	2	1	2	1	4
Multitherapy	0	2	0	7	0	9
Current use	0	3	1	4	1	7
Past use	0	1	0	5	0	6
Biologic DMARDS	0	4	0	0	0	4
Other DMARDS	1	7	5	33	6	40

Table B.8

Frequency of lymphoma
for newer DMARDs and methotrexate monotherapy
(Rate ratios not estimable)

DMARD use in the prior year	PHARMETRICS		PROTOCARE		COMBINED	
	Cases (n=3)	Controls (n=30)	Cases (n=2)	Controls (n=20)	Cases (n=5)	Controls (n=50)
Methotrexate only	0	8	0	6	0	14
Leflunomide	0	5	0	3	0	8
Monotherapy	0	3	0	0	0	3
Multitherapy	0	2	0	3	0	5
Current use	0	2	0	2	0	4
Past use	0	3	0	1	0	4
Biologic DMARDS	1	3	0	1	1	4
Other DMARDS	1	8	2	10	3	18

APPENDIX C

RESULTS OF ADVERSE EVENTS DEFINED WITHOUT REQUIREMENT OF HOSPITALISATION

(EXPANDED DEFINITION)

Table C.1

Crude and adjusted rate ratios of any adverse event for newer DMARDs relative to methotrexate monotherapy

(EXPANDED DEFINITION)

DMARD use in the prior year	PHARMETRICS				PROTOCARE				COMBINED			
	Cases (n=1118)	Controls (n=11180)	Crude RR	Adjusted* RR (95% CI)	Cases (n=361)	Controls (n=3610)	Crude RR	Adjusted* RR (95% CI)	Cases (n=463)	Controls (n=4630)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	311	3757	1.0	Reference	167	1677	1.0	Reference	478	5434	1.0	Reference
Leflunomide	171	1566	1.3	1.3 (1.0-1.6)	44	370	1.2	1.2 (0.8-1.7)	215	1936	1.3	1.2 (1.0-1.5)
Monotherapy	85	881	1.2	1.1 (0.9-1.4)	18	182	1.0	0.9 (0.5-1.5)	103	1063	1.1	1.0 (0.8-1.3)
Multitherapy	86	685	1.5	1.5 (1.1-1.9)	26	188	1.4	1.4 (0.9-2.3)	112	873	1.5	1.5 (1.2-1.8)
Current use	123	1271	1.2	1.1 (0.9-1.4)	28	267	1.1	1.0 (0.7-1.6)	151	1538	1.1	1.1 (0.9-1.3)
Past use	48	295	2.0	1.8 (1.3-2.5)	16	103	1.6	1.4 (0.8-2.5)	64	398	1.9	1.7 (1.2-2.2)
Biologic DMARDS	117	998	1.4	1.4 (1.1-1.8)	4	34	1.2	1.5 (0.5-4.6)	121	1032	1.4	1.4 (1.1-1.7)
Other DMARDS	460	4330	1.3	1.2 (1.1-1.4)	125	1304	1.0	1.0 (0.7-1.3)	585	5634	1.2	1.2 (1.0-1.3)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table C.2

Crude and adjusted rate ratios of any hepatic event for newer DMARDs relative to methotrexate monotherapy

(EXPANDED DEFINITION)

DMARD use in the prior year	PHARMETRICS				PROTOCARE				COMBINED			
	Cases (n=332)	Controls (n=3320)	Crude RR	Adjusted* RR (95% CI)	Cases (n=90)	Controls (n=8886)	Crude RR	Adjusted* RR (95% CI)	Cases (n=422)	Controls (n=12206)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	93	1041	1.0	Reference	45	4073	1.0	Reference	138	5114	1.0	Reference
Leflunomide	45	499	1.0	1.0 (0.7-1.4)	11	874	1.1	1.0 (0.5-1.9)	56	1373	1.0	1.0 (0.7-1.3)
Monotherapy	23	274	0.9	0.8 (0.5-1.4)	5	425	1.1	0.9 (0.4-2.3)	28	699	0.9	0.8 (0.5-1.3)
Multitherapy	22	225	1.1	1.1 (0.7-1.9)	6	449	1.2	1.0 (0.4-2.5)	28	674	1.1	1.1 (0.7-1.7)
Current use	32	387	0.9	0.9 (0.6-1.4)	6	633	0.8	0.7 (0.3-1.8)	38	1020	0.9	0.9 (0.6-1.3)
Past use	13	112	1.3	1.0 (0.5-2.0)	5	241	1.9	1.5 (0.6-4.0)	18	353	1.4	1.2 (0.7-2.0)
Biologic DMARDS	38	283	1.5	1.6(1.1-2.5)	2	76	2.4	2.5(0.6-10.7)	40	359	1.5	1.6 (1.1-2.4)
Other DMARDS	146	1360	1.2	1.1 (0.9-1.5)	29	3325	0.8	0.7 (0.5-1.2)	175	4685	1.1	1.0 (0.8-1.3)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table C.3

Crude and adjusted rate ratios of any hematologic event for newer DMARDs relative to methotrexate monotherapy

(EXPANDED DEFINITION)

DMARD use in the prior year	PHARMETRICS				PROTOCARE				COMBINED			
	Cases (n=533)	Controls (n=5330)	Crude RR	Adjusted* RR (95% CI)	Cases (n=155)	Controls (n=1550)	Crude RR	Adjusted* RR (95% CI)	Cases (n=688)	Controls (n=6880)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	165	1801	1.0	Reference	71	700	1.0	Reference	236	2501	1.0	Reference
Leflunomide	89	724	1.4	1.3 (1.0-1.8)	20	162	1.2	1.2 (0.7-2.2)	109	886	1.3	1.3 (1.0-1.7)
Monotherapy	40	414	1.1	1.0 (0.7-1.5)	6	87	0.7	0.7 (0.3-1.7)	46	501	1.0	1.0 (0.7-1.4)
Multitherapy	49	310	1.8	1.8 (1.2-2.5)	14	75	1.9	1.9 (1.0-3.9)	63	385	1.8	1.8 (1.3-2.4)
Current use	66	561	1.3	1.3 (0.9-1.7)	12	113	1.0	1.1 (0.5-2.1)	78	674	1.2	1.2 (0.9-1.6)
Past use	23	163	1.6	1.5 (1.0-2.5)	8	49	1.6	1.6 (0.7-3.8)	31	212	1.6	1.6 (1.0-2.4)
Biologic DMARDS	50	415	1.3	1.4 (1.0-2.0)	3	31	1.0	1.4 (0.4-4.9)	53	446	1.3	1.4 (1.0-1.9)
Other DMARDS	198	2156	1.0	1.0 (0.8-1.2)	51	556	0.9	0.9 (0.6-1.4)	249	2712	1.0	1.0 (0.8-1.2)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table C.4

Crude and adjusted* rate ratios of any pancreatics event for newer DMARDs relative to methotrexate monotherapy

(EXPANDED DEFINITION)

DMARD use in the prior year	PHARMETRICS				PROTOCARE				COMBINED			
	Cases (n=110)	Controls (n=1100)	Crude RR	Adjusted* RR (95% CI)	Cases (n=69)	Controls (n=6850)	Crude RR	Adjusted* RR (95% CI)	Cases (n=179)	Controls (n=7950)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	21	354	1.0	Reference	30	3231	1.0	Reference	51	3585	1.0	Reference
Leflunomide	20	154	2.2	1.9 (1.0-3.8)	10	642	1.7	1.8 (0.9-3.9)	30	796	1.9	1.7 (1.0-2.8)
Monotherapy	13	82	2.7	2.3 (1.1-4.9)	5	290	1.9	1.9 (0.7-5.2)	18	372	2.2	1.9 (1.1-3.5)
Multitherapy	7	72	1.7	1.5 (0.6-3.8)	5	352	1.5	1.7 (0.7-4.6)	12	424	1.5	1.4 (0.7-2.9)
Current use	15	125	2.1	1.9 (0.9-3.9)	7	443	1.7	1.8 (0.8-4.3)	22	568	1.8	1.7 (1.0-2.9)
Past use	5	29	3.0	2.1(0.7-6.4)	3	199	1.6	1.8 (0.5-6.3)	8	228	2.2	1.8 (0.8-4.2)
Biologic DMARDS	12	104	2.0	2.0 (0.9-4.4)	0	76	0.0	0.0 (ne)	12	180	1.5	1.5 (0.8-3.1)
Other DMARDS	49	424	1.9	2.0 (1.2-3.5)	25	2454	1.1	1.2 (0.7-2.1)	74	2878	1.5	1.6 (1.1-2.3)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.

Table C.5

Crude and adjusted rate ratios of any skin reaction for newer DMARDs relative to methotrexate monotherapy

(EXPANDED DEFINITION)

DMARD use in the prior year	PHARMETRICS				PROTOCARE				COMBINED			
	Cases (n=30)	Controls (n=2930)	Crude RR	Adjusted* RR (95% CI)	Cases (n=1)	Controls (n=100)	Crude RR	Adjusted RR (95% CI)	Cases (n=31)	Controls (n=2940)	Crude RR	Adjusted* RR (95% CI)
Methotrexate only	7	1027	1.0	Reference	0	29			7	1056	1.0	Refence
Leflunomide	4	399	1.5	1.4 (0.4-4.9)	0	11			4	410	1.5	1.3 (0.4-4.7)
Monotherapy	3	229	1.9	1.9 (0.5-7.8)	0	7			3	236	1.9	1.8 (0.4-7.3)
Multitherapy	1	170	0.9	0.8 (0.1-6.4)	0	4			1	174	0.9	0.7 (0.1-6.3)
Current use	4	336	1.8	1.6 (0.5-5.8)	0	6			4	342	1.8	1.6 (0.5-5.7)
Past use	0	63	0.0	0.0 (ne)	0	5			0	68	0.0	0.0 (ne)
Biologic DMARDS	2	255	1.2	0.8 (0.1-4.5)	0	0			2	255	1.2	1.0 (0.2-5.0)
Other DMARDS	14	1167	1.8	1.6 (0.6-4.2)	1	49			15	1216	1.9	1.8 (0.7-4.4)

* Adjusted for age, gender, non use of DMARDs in the year prior to the index date, use of NSAIDS, COX-2 inhibitors, glucocorticoids and co-morbidity.